63

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(54) Title: A BUILDING BLOCK FORMING A C-C OR A C-HETERO ATOM BOND UPONREACTION

(57) Abstract: A building block having the dual capabilities of transferring genetic information and functional entity precursor to a recipient reactive group is disclosed. The building block may be used in the generation of a single complex or libraries of different complexes, wherein the complex comprises an encoded molecule linked to an encoding element. Libraries of complexes are useful in the quest for pharmaceutically active compounds.

Title

A BUILDING BLOCK FORMING A C-C OR C-HETERO ATOM BOND UPON REACTION.

Technical Field of the Invention

The present invention relates to a building block comprising a complementing element and a precursor for a functional entity. The building block is designed to transfer the functional entity precursor with an adjustable efficiency to a recipient reactive group upon recognition between the complementing element and an encoding element associated with the reactive group. The invention also relates to a method for transferring a functional entity precursor to recipient a reactive group.

Background

The transfer of a chemical entity from one mono-, di- or oligonucleotide to another has been considered in the prior art. Thus, N. M. Chung *et al.* (Biochim. Biophys. Acta,1971, 228,536-543) used a poly(U) template to catalyse the transfer of an acetyl group from 3'-O-acetyladenosine to the 5'-OH of adenosine. The reverse transfer, i.e. the transfer of the acetyl group from a 5'-O-acetyladenosine to a 3'-OH group of another adenosine, was also demonstrated.

Walder *et al.* Proc. Natl. Acad. Sci. USA, 1979, 76, 51-55 suggest a synthetic procedure for peptide synthesis. The synthesis involves the transfer of nascent immobilized polypeptide attached to an oligonucleotide strand to a precursor amino acid attached to an oligonucleotide. The transfer comprises the chemical attack of the amino group of the amino acid precursor on the substitution labile peptidyl ester, which in turn results in an acyl transfer. It is suggested to attach the amino acid precursor to the 5' end of an oligonucleotide with a thiol ester linkage.

The transfer of a peptide from one oligonucleotide to another using a template is disclosed in Bruick RK et al. Chemistry & Biology, 1996, 3:49-56. The carboxy terminal of the peptide is initially converted to a thioester group and subsequently transformed to an activated thioester upon incubation with Ellman's reagent. The activated thioester is reacted with a first oligo, which is 5'-thiol-terminated, resulting in the formation of a thio-ester linked intermediate. The first oligonucleotide and a

second oligonucleotide having a 3' amino group is aligned on a template such that the thioester group and the amino group are positioned in close proximity and a transfer is effected resulting in a coupling of the peptide to the second oligonucleotide through an amide bond.

Summary of the Invention

The present invention relates to a building block of the general formula:

Complementing Element – Linker – Carrier – C-F-connecting group - Functional entity precursor

capable of transferring a Functional entity precursor to a recipient reactive group, wherein

Complementing Element is a group identifying the Functional entity precursor,

Linker is a chemical moiety comprising a **spacer** and a **S-C-connecting group**, wherein the spacer is a valence bond or a group distancing the Functional entity precursor to be transferred from the complementing element and the S-C-connecting group connects the spacer with the Carrier

Carrier is arylene, heteroarylene, C_1-C_6 alkylene, C_1-C_6 alkenylene, C_1-C_6 alkynylene, or -$(CF_2)_m$- substituted with 0-3 R^1 wherein m is an integer between 1 and 10;

R^1 are independently selected from -H, -OR^2, -NR^2_2, -Halogen, -NO_2, -CN, -C(Halogen)$_3$, -C(O)R^2, -C(O)NHR^2, C(O)NR^2_2, -NC(O)R^2, -S(O)$_2NHR^2$, -S(O)$_2NR^2_2$, -S(O)$_2R^2$, –P(O)$_2$-R^2, –P(O)- R^2, –S(O)- R^2, P(O)-OR^2, –S(O)-OR^2, -$N^+R^2_3$, wherein R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl,

C-F-connecting group is chosen from the group consisting of –SO_2-O-, -O-SO_2-O-, -C(O)-O-, -S^+(R^3RRrr)-, -C-U-C(V)-O-, -$P^+(W)_2$-O-, -P(W)-O- where U is -$C(R^2)_2$-, -NR^2- or –O-; V is =O or =NR^2 and W is -OR^2 or –$N(R^2)_2$

Functional entity precursor is -C(H)(R^3)-R^4 or functional entity precursor is heteroaryl or aryl optionally substituted with one or more substituents belonging to the group comprising R^3 and R^4.

Wherein R^3 and R^4 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $SnR^5R^6R^7$, Sn(OR^5)R^6R^7, Sn(OR^5)(OR^6)R^7, BR^5R^6, B(OR^5)R^6, B(OR^5)(OR^6), halogen, CN, CNO, C(halogen)$_3$,

OR^5, OC(=O)R^5, OC(=O)OR^5, OC(=O)NR^5R^6, SR^5, S(=O)R^5, S(=O)$_2R^5$, S(=O)$_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, NR^5C(=O)R^6, NR^5C(=O)OR^6, NR^5C(=O)NR^6R^7, NC, P(=O)(OR^5)OR^6, $P^+R^5R^6R^7$, C(=O)R^5, C(=NR^5)R^6, C(=NOR^5)R^6, C(=NNR^5R^6), C(=O)OR^5, C(=O)NR^5R^6, C(=O)NR^5OR^6, C(=O)$NR^5NR^6R^7$, C(=NR^5)NR^6R^7, C(=NOR^5)NR^6R^7 or R^8,

wherein,

R^5, R^6, and R^7 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CNO, C(halogen)$_3$, =O, OR^8, OC(=O)R^8, OC(=O)OR^8, OC(=O)NR^8R^9, SR^8, S(=O)R^8, S(=O)$_2R^8$, S(=O)$_2NR^8R^9$, NO_2, N_3, NR^8R^9, $N^+R^8R^9R^{10}$, NR^5OR^6, $NR^5NR^6R^7$, NR^8C(=O)R^9, NR^8C(=O)OR^9, NR^8C(=O)NR^9R^{10}, NC, P(=O)(OR^8)OR^9, $P^+R^5R^6R^7$, C(=O)R^8, C(=NR^8)R^9, C(=NOR^8)R^9, C(=NNR^8R^9), C(=O)OR^8, C(=O)NR^8R^9, C(=O)NR^8OR^9 C(=NR^5)NR^6R^7, C(=NOR^5)NR^6R^7or C(=O)$NR^8NR^9R^{10}$, wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

wherein,

R^8, R^9, and R^{10} independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl and wherein R^8 and R^9 may together form a 3-8 membered heterocyclic ring or R^8 and R^{10} may together form a 3-8 membered heterocyclic ring or R^9 and R^{10} may together form a 3-8 membered heterocyclic ring.

In the present description and claims, the direction of connections between the various components of a building block should be read left to right. For example an S-C-connecting group –C(=O)-NH- is connected to a Spacer through the carbon atom on the left and to a Carrier through the nitrogen atom on the right hand side.

The term "C_3-C_7 cycloheteroalkyl" as used herein refers to a radical of totally saturated heterocycle like a cyclic hydrocarbon containing one or more heteroatoms selected from nitrogen, oxygen, phosphor, boron and sulphur independently in the cycle such as pyrrolidine (1- pyrrolidine; 2- pyrrolidine; 3- pyrrolidine; 4- pyrrolidine; 5- pyrrolidine); pyrazolidine (1- pyrazolidine; 2- pyrazolidine; 3- pyrazolidine; 4-pyrazolidine; 5-pyrazolidine); imidazolidine (1- imidazolidine; 2- imida-

zolidine; 3- imidazolidine; 4- imidazolidine; 5- imidazolidine); thiazolidine (2- thiazolidine; 3- thiazolidine; 4- thiazolidine; 5- thiazolidine); piperidine (1- piperidine; 2-piperidine; 3- piperidine; 4- piperidine; 5- piperidine; 6- piperidine); piperazine (1-piperazine; 2- piperazine; 3- piperazine; 4- piperazine; 5- piperazine; 6-piperazine); morpholine (2- morpholine; 3- morpholine; 4- morpholine; 5- morpholine; 6- morpholine); thiomorpholine (2- thiomorpholine; 3- thiomorpholine; 4-thiomorpholine; 5- thiomorpholine; 6- thiomorpholine); 1,2-oxathiolane (3-(1,2-oxathiolane); 4-(1,2-oxathiolane); 5-(1,2-oxathiolane); 1,3-dioxolane (2-(1,3-dioxolane); 4-(1,3-dioxolane); 5-(1,3-dioxolane); tetrahydropyrane; (2-tetrahydropyrane; 3-tetrahydropyrane; 4-tetrahydropyrane; 5-tetrahydropyrane; 6-tetrahydropyrane); hexahydropyridazine (1-(hexahydropyridazine); 2-(hexahydropyridazine); 3-(hexahydropyridazine); 4-(hexahydropyridazine); 5-(hexahydropyridazine); 6-(hexahydropyridazine)), [1,3,2]dioxaborolane, [1,3,6,2]dioxazaborocane

The term "aryl" as used herein includes carbocyclic aromatic ring systems of 5-7 carbon atoms. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems as well as up to four fused fused aromatic- or partially hydrogenated rings, each ring comprising 5-7 carbon atoms.

The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing, in addition to 2-18 carbon atoms, one or more heteroatoms selected from nitrogen, oxygen and sulphur such as furyl, thienyl, pyrrolyl, heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated below.

The terms "aryl" and "heteroaryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-

pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl).

The Functional Entity carries elements used to interact with host molecules and optionally reactive elements allowing further elaboration of an encoded molecule of a library. Interaction with host molecules like enzymes, receptors and polymers is typically mediated through van der waal's interactions, polar- and ionic interactions and pi-stacking effects. Substituents mediating said effects may be masked by methods known to an individual skilled in the art (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley & Sons: New York, 1999.) to avoid undesired interactions or reactions during the preparation of the individual building blocks and during library synthesis. Analogously, reactive elements may be

masked by suitably selected protection groups. It is appreciated by one skilled in the art that by suitable protection, a functional entity may carry a wide range of substitutents.

The Functional Entity Precursor is a masked Functional Entity that is incorporated into an encoded molecule. After incorporation, reactive elements of the Functional Entity may be revealed by un-masking allowing further synthetic operations. Finally, elements mediating recognition of host molecules may be un-masked.

In a certain aspect of the invention, **Functional entity precursor** is $-C(H)(R^{11})-R^{11'}$ or functional entity precursor is heteroaryl or aryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3 R^{15}, wherein

R^{11} and $R^{11'}$ are independently H, or selected among the group consisting of a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^{12}, 0-3 R^{13} and 0-3 R^{15},

or R^{11} and $R^{11'}$ are C_1-C_3 alkylene-NR^{12}_2, C_1-C_3 alkylene-$NR^{12}C(O)R^{16}$, C_1-C_3 alkylene-$NR^{12}C(O)OR^{16}$, C_1-C_2 alkylene-O-NR^{12}_2, C_1-C_2 alkylene-O-$NR^{12}C(O)R^{16}$, C_1-C_2 alkylene-O-$NR^{12}C(O)OR^{16}$ substituted with 0-3 R^{15},

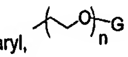
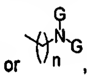
where R^{12} is H or selected independently among the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{13} and 0-3 R^{15},

R^{13} is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, -NHOH, $-NHNHR^{17}$, $-C(O)R^{17}$, $-SnR^{17}_3$, $-B(OR^{17})_2$, $-P(O)(OR^{17})_2$ or the group consisting of C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^{14},

where R^{14} is independently selected from $-NO_2$, $-C(O)OR^{17}$, $-COR^{17}$, -CN, $-OSiR^{17}_3$, $-OR^{17}$ and $-NR^{17}_2$;

R^{15} is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^{17}$, $-NR^{17}_2$, $-NR^{17}-C(O)R^{18}$, $-NR^{17}-C(O)OR^{18}$, $-SR^{17}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-COOR^{17}$, $-C(O)NR^{17}_2$ and $-S(O)_2NR^{17}_2$,

R^{16} is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, –NO_2, $-R^2$, $-OR^2$, $-SiR^2_3$;

R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl,  or , G is H or C_1-C_6 alkyl and n is 1,2,3 or 4.

The function of the carrier is to ensure the transferability of the functional entity precursor. To adjust the transferability a skilled chemist can design suitable substitutions of the carrier by evaluation of initial attempts. The transferability may be adjusted in response to the chemical composition of the functional entity precursor, to the nature of the complementing element, to the conditions under which the transfer and recognition is performed, etc.

In a preferred embodiment, the carrier is selected from the group consisting of arylene, heteroarylene or $-(CF_2)_m$- substituted with 0-3 R^1 wherein m is an integer between 1 and 10, and C-F-connecting group is $-SO_2-O-$. Due to the high reactivity of such compounds a broad range of recipient reactive groups may be employed in the construction of carbon-carbon bonds or carbon-hetero atom bonds.

In another preferred embodiment of the invention, the carrier is $-(CF_2)_m$- wherein m is an integer between 1 and 10, the C-F-connecting group is $-SO_2-O-$; and the functional entity precursor is aryl or heteroaryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3 R^{15}.

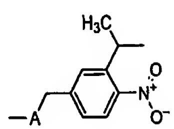
The C-F-connecting group determines in concert with the carrier the transferability of the functional entity precursor. In a preferred embodiment, the **C-F-connecting group** is $-S^+(R^{11})$-,

In another preferred embodiment, the **C-F-connecting group** is chosen from the group consisting of $-SO_2-O-$, and $-S^+(R^{17})$-; wherein R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl.

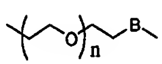
In the presence of a catalyst comprising transition metals such as Pd, Ni or Cu, an aromatic moiety may be transferred from the C-F-connecting group to a recipient reactive group. Further, the transfer may be initiated by adding the catalyst, independently of the annealing of encoding - and complementing elements.

The S-C-connecting group provide a means for connecting the Spacer and the Carrier. As such it is primarily of synthetic convenience and does not influence the function of a building block.

The spacer serves to distance the functional entity precursor to be transferred from the bulky complementing element. Thus, when present, the identity of the spacer is not crucial for the function of the building block. It may be desired to have a spacer which can be cleaved by light. In this case, the spacer is provided with e.g. the group



In the event an increased hydrophilicity is desired the spacer may be provided with a polyethylene glycol part of the general formula:



In a preferred embodiment, the complementing element serves the function of transferring genetic information e.g. by recognising a coding element. The recognition implies that the two parts are capable of interacting in order to assemble a complementing element – coding element complex. In the biotechnological field a variety of interacting molecular parts are known which can be used according to the invention. Examples include, but are not restricted to protein-protein interactions, protein-polysaccharide interactions, RNA-protein interactions, DNA-DNA interactions, DNA-RNA interactions, RNA-RNA interactions, biotin-streptavidin interactions, enzyme-ligand interactions, antibody-ligand interaction, protein-ligand interaction, etc.

The interaction between the complementing element and coding element may result in a strong or a weak bonding. If a covalent bond is formed between the parties of the affinity pair the binding between the parts can be regarded as strong, whereas the establishment of hydrogen bondings, interactions between hydrophobic do-

mains, and metal chelation in general results in weaker bonding. In general relatively weak bonding is preferred. In a preferred aspect of the invention, the complementing element is capable of reversible interacting with the coding element so as to provide for an attachment or detachment of the parts in accordance with the changing conditions of the media.

In a preferred aspect of the invention, the interaction is based on nucleotides, i.e. the complementing element is a nucleic acid. Preferably, the complementing element is a sequence of nucleotides and the coding element is a sequence of nucleotides capable of hybridising to the complementing element. The sequence of nucleotides carries a series of nucleobases on a backbone. The nucleobases may be any chemical entity able to be specifically recognized by a complementing entity. The nucleobases are usually selected from the natural nucleobases (adenine, guanine, uracil, thymine, and cytosine) but also the other nucleobases obeying the Watson-Crick hydrogen-bonding rules may be used, such as the synthetic nucleobases disclosed in US 6,037,120. Examples of natural and non-natural nucleobases able to perform a specific pairing are shown in figure 2. The backbone of the sequence of nucleotides may be any backbone able to aggregate the nucleobases is a sequence. Examples of backbones are shown in figure 4. In some aspects of the invention the addition of non-specific nucleobases to the complementing element is advantegeous, figure 3

The coding element can be an oligonucleotide having nucleobases which complements and is specifically recognised by the complementing element, i.e. in the event the complementing element contains cytosine, the coding element part contains guanine and visa versa, and in the event the complementing element contains thymine or uracil the coding element contains adenine.

The complementing element may be a single nucleobase. In the generation of a library, this will allow for the incorporation of four different functional entities into the template-directed molecule. However, to obtain a higher diversity a complementing element preferably comprises at least two and more preferred at least three nucleotides. Theoretically, this will provide for 4^2 and 4^3, respectively, different functional entities uniquely identified by the complementing element. The complementing element will usually not comprise more than 100 nucleotides. It is preferred to have complementing elements with a sequence of 3 to 30 nucleotides.

The building blocks of the present invention can be used in a method for transferring a functional entity precursor to a recipient reactive group, said method comprising the steps of

providing one or more building blocks as described above and

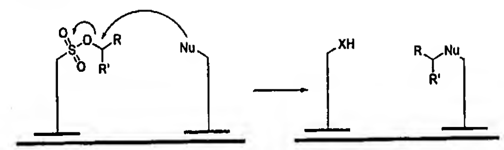
contacting the one or more building blocks with a corresponding encoding element associated with a recipient reactive group under conditions which allow for a recognition between the one or more complementing elements and the encoding elements, said contacting being performed prior to, simultaneously with, or subsequent to a transfer of the functional entity precursor to the recipient reactive group.

The encoding element may comprise one, two, three or more codons, i.e. sequences that may be specifically recognised by a complementing element. Each of the codons may be separated by a suitable spacer group. Preferably, all or at least a majority of the codons of the template are arranged in sequence and each of the codons are separated from a neighbouring codon by a spacer group. Generally, it is preferred to have more than two codons on the template to allow for the synthesis of more complex encoded molecules. In a preferred aspect of the invention the number of codons of the encoding element is 2 to 100. Still more preferred are encoding elements comprising 3 to 10 codons. In another aspect, a codon comprises 1 to 50 nucleotides and the complementing element comprises a sequence of nucleotides complementary to one or more of the encoding sequences.

The recipient reactive group may be associated with the encoding element in any appropriate way. Thus, the reactive group may be associated covalently or non-covalently to the encoding element. In one embodiment the recipient reactive group is linked covalently to the encoding element through a suitable linker which may be separately cleavable to release the reaction product. In another embodiment, the reactive group is coupled to a complementing element, which is capable of recognising a sequence of nucleotides on the encoding element, whereby the recipient reactive group becomes attached to the encoding element by hybridisation. Also, the recipient reactive group may be part of a chemical scaffold, i.e. a chemical entity having one or more reactive groups available for receiving a functional entity precursor from a building block.

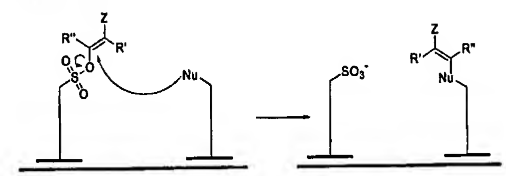
The recipient reactive group may be any group able to participate in cleaving the bond between the carrier and the functional entity precursor to release the functional entity precursor. Typically, the recipient reactive group is a nucleophilic atom such as S, N, O, C or P. Scheme 1a shows the transfer of an alkyl group and scheme 1b shows the transfer of an vinyl group..

Scheme 1a



Nu = Oxygen-, Nitrogen-, Sulfur- and Carbon Nucleophiles

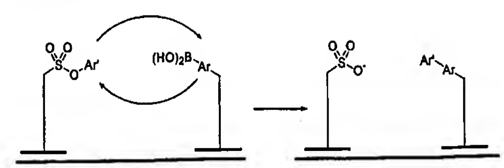
Scheme 1b



Z = CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F
Nu = Oxygen-, Nitrogen-, Sulfur- and Carbon Nucleophiles

Alternatively, the recipient reactive group is a organometallic compound as shown in scheme 2.

Scheme 2



According to a preferred aspect of the invention the building blocks are used for the formation of a library of compounds. The complementing element of the building block is used to identify the functional entity. Due to the enhanced proximity between reactive groups when the complementing entity and the encoding element are

contacted, the functional entity precursor together with the identity programmed in the complementing element is transferred to the encoding element associated with recipient reactive group. Thus, it is preferred that the sequence of the complementing element is unique in the sense that the same sequence is not used for another functional entity. The unique identification of the functional entity enable the possibility of decoding the encoding element in order to determine the synthetic history of the molecule formed. In the event two or more functional entities have been transferred to a scaffold, not only the identity of the transferred functional entities can be determined. Also the sequence of reaction and the type of reaction involved can be determined by decoding the encoding element. Thus, according to a preferred embodiment of the invention, each different member of a library comprises a complementing element having a unique sequence of nucleotides, which identifies the functional entity.

Brief description of the drawings

Figure 1. Two setups for Functional Entity Transfer
Figure 2. Examples of specific base pairing
Figure 3. Example of non-specific base-pairing
Figure 4. Backbone examples
Figure 5 Three examples of building blocks

Detailed Description of the Invention

A building block of the present invention is characterized by its ability to transfer its functional entity precursor to a recipient reactive group. This is done by forming a new covalent bond between the recipient reactive group and cleaving the bond between the carrier moiety and the functional entity precursor of the building block.

Two setups for generalized functional entity precursor transfer from a building block are depicted in figure 1. In the first example, one complementing element of a building block recognizes a coding element carrying another functional entity precursor, hence bringing the functional entities in close proximity. This results in a reaction between functional entity precursor 1 and 2 forming a covalent bond between these concurrent with the cleavage of the bond between functional entity precursor 2 and its linker. In the second example, a template brings together two building blocks resulting in functional entity precursor transfer from one building block to the other.

Figure 5 illustrates three specific compounds according to the Invention. For illustrative purposes the individual features used in the claims are indicated. The upper compound is an example of a building block wherein the linker is backbone attached at the 3'-position. The first part of the linker, i.e. the spacer, is an aliphatic chain ending in a nitrogen atom. The nitrogen atom bridges to the S-C-connecting group, which is an N-acylated arylmethyleamine. The carrier attached to the left hand side carbonyl group of the S-C-connecting group is a benzene ring holding the C-F Connecting group in the para position. The C-F Connecting group is a positively charged sulfur atom which is attached to the Functional Entity Precursor, in this case a benzyl group. When the building block is presented to a nucleophilic recipient reactive group, such an amine or a thiol, Functional Entity Precursor is transferred to benzylate the recipient reactive group.

The middle compound illustrates a 5' attachment of a linker. The linker is linked through a phosphate group and extends into a three membered aliphatic chain. Through another phosphate group and a PEG linker the complementing element is linked via an amide bond to the Carrier. When the building block is presented to a nucleophile the Functional Entity Precursor is transferred resulting in an alkylation of the nucleophile.

The lower compound illustrates a nucleobase attachment of the linker. The linker attaches to the 5 position of a pyrimidine type nucleobase and extents through an α – β unsaturated N-methylated amide to the S-C-connecting group, which is a 4-amino methyl benzoic acid derivative. The functional entity precursor can be transferred to a nucleophilic recipient reactive group e.g. an amine or a thiol forming an allylic amine or thiol.

According to the invention, the functional entity precursor is of the formula $-C(H)(R^3)-R^4$ or functional entity precursor is heteroaryl or aryl optionally substituted with one or more substituents belonging to the group comprising R^3 and R^4. In a further preferred embodiment,
R^3 and R^4 independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of

SnR^5R^6,R^7, $Sn(OR^5)R^6R^7$, $Sn(OR^5)(OR^6)R^7$, BR^5R^6, $B(OR^5)R^6$, $B(OR^5)(OR^6)$, halogen, CN, CNO, $C(halogen)_3$, =O, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, NC, $P(=O)(OR^5)OR^6$, $P^+R^5R^6R^7$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in another prefered embodiment,

R^3 and R^4 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, $C(halogen)_3$, =O, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $P(=O)(OR^5)OR^6$, $C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $P(=O)(OR^5)OR^6$,

$C(=O)R^5$, $C(=NR^5)R^6$, $C(=NOR^5)R^6$, $C(=NNR^5R^6)$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$, $C(=O)NR^5NR^6R^7$, $C(=NR^5)NR^6R^7$, $C(=NOR^5)NR^6R^7$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered het-

erocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group

consisting of F, Cl, CN, CF_3, =O, OR^6, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is H, phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,

R^3 and R^4 independently is H, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, methyl, ethyl, propyl or butyl and wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

in still another prefered embodiment,
R^3 and R^4 independently is methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

in still another prefered embodiment,
R^3 and R^4 independently is aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,
wherein,
R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

in still another prefered embodiment,
R^3 and R^4 independently is phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$,

NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

in still another prefered embodiment,

R^3 and R^4 independently is phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

in still another prefered embodiment,

R^3 and R^4 independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

in still another prefered embodiment,

R^3 and R^4 independently is methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

in still another prefered embodiment,

R^3 and R^4 independently is aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

in still another prefered embodiment,

R^3 and R^4 independently is phenyl, naphtyl, thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

in still another prefered embodiment,

R^3 and R^4 independently is phenyl or naphtyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

in still another prefered embodiment,

R^3 and R^4 independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolinyl optionally substituted with one or more substituents selected from the group consisting of F, Cl, CN, CF_3, =O, OR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, NR^5R^6, $NR^5C(=O)R^6$,

$NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, $C(=O)R^5$, $C(=NOR^5)R^6$, $C(=O)OR^5$, $C(=O)NR^5R^6$, $C(=O)NR^5OR^6$ or R^8,

wherein,

R^5, R^6, R^7 and R^8 independently is H, phenyl, naphthyl, thienyl, furyl, pyridinyl, quinolinyl or isoquinolinyl,

in still another prefered embodiment,
R^3 and R^4 independently is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl or heteroaryl

in still another prefered embodiment,
R^3 and R^4 independently is H,

in still another prefered embodiment,
R^3 and R^4 independently is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or C_3-C_7 cycloheteroalkyl,

in still another prefered embodiment,
R^3 and R^4 independently is methyl, ethyl, propyl or butyl

in still another prefered embodiment
R^3 and R^4 independently is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl

in still another prefered embodiment
R^3 and R^4 independently is aziridinyl, pyrrolidinyl, piperidinyl or morpholinyl

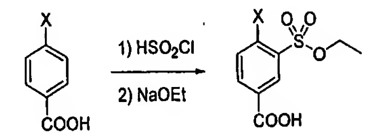
in still another prefered embodiment,
R^3 and R^4 independently is aryl or heteroaryl

in still another prefered embodiment,
R^3 and R^4 independently is phenyl or naphthyl

in still another prefered embodiment,
R^3 and R^4 independently is thienyl, furyl, pyridyl, quinolinyl or isoquinolyl

Experimental section

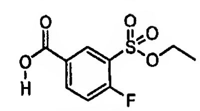
<u>General Procedure 1: Preparation of Carrier-Functional entity reagents:</u>



The 4-halobenzoic acid (25 mmol) is added to a ice cooled solution of chloro sulfonic acid (140 mmol). The mixture is slowly heated to reflux and left at reflux for 2-3 hours. The mixture is added to 100 mL ice and the precipitate collected by filtration. The filtrate is washed with water (2 x 50 mL) and the dried *in vacuo* affording the corresponding sulfonoyl chloride in 60-80% yield. The 3-chlorosulfonyl-4-halobenzoic acid derivate (5 mmol) is dissolved in EtOH (5 mL) and added to a ice cooled mixture of NaOEt (10 mL, 2M). The mixture is stirred o/n at rt. Acetic acid (40 mmol) is added and the mixture is evaporated *in vacuo*. Water (10 mL) is added and pH adjusted to pH = 2 (using 1M HCl). The product is extracted with DCM (2 x25 mL), dried over Na_2SO_4 and evaporated *in vacuo* affording the desired products.

Example 1 (General procedure (1))

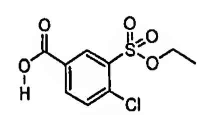
3-Ethoxysulfonyl-4-fluorobenzoic acid



^{1}H-NMR (DMSO-d_6): δ 8.49 (d, 1H), 7.85 (dd, 1H), 7.5 (d, 1H), 4.32 (q, 2H), 1.32 (t, 3H)

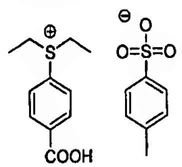
Example 2 (General procedure (1))

4-chloro-3-Ethoxysulfonylbenzoic acid



^{1}H-NMR (DMSO-d_6): δ 8.49 (d, 1H), 7.85 (dd, 1H), 7.5 (d, 1H), 4.32 (q, 2H), 1.32 (t, 3H)

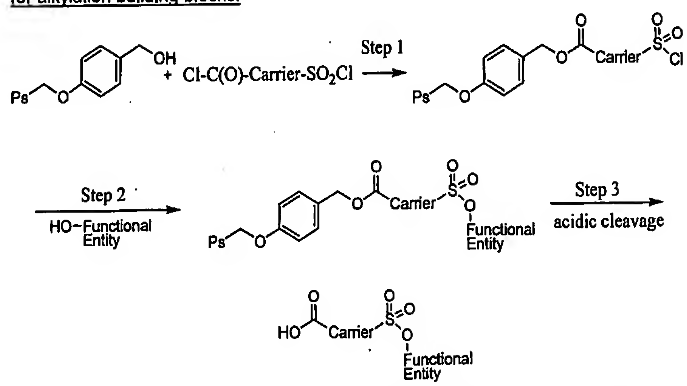
Example 3



4-Methylsulfanyl benzoic acid (0.5g, 2.97 mmol, commercially available from Aldrich, cat no. 145521) was added to methyl p-toluene solfunate (0.61g, 3.27 mmol). The mixture was heated to 140 °C for 1 hour in a sealed vessel. After cooling to rt the mixture was trituated with diethyl ether. Filtration and drying *in vacuo* yielded 844 mg (80%) of the desired product (>95% pure by ^{1}H nmr).

^{1}H nmr (DMSO-*d6*): 8.20-8.10 (m, 4H), 7.45 (d, 2H), 7.08 (d, 2H), 3.29 (s, 6H), 2.30 (s, 3H).

<u>General Procedure 2: Solid phase preparation of Carrier-Functional entity reagents for alkylation building blocks:</u>



Ps = Polystyrene resin. Alternatively other acid labile linkers may be employed.

Step 1:

A polystyrene resin with a wang linker (4-hydroxymethylphenol linker) (50 mg ~ 50 umol), a bi-functional carrier (200 umol, 4 equiv) in a solvent such as THF, DCM,

DCE, DMF, NMP or a mixture thereof (500 uL) and a base such as TEA, DIEA, pyridine (400 umol, 8 equiv), optionally in the presence of DMAP (100 umol), are allowed to react at temperatures between -20 °C and 60 °C, preferably between 0 °C and 25 °C, for 1-24 h, preferably 1-4 h. The resin is washed with the solvent composition used during the reaction (5x1 mL) and used in the following step.

Step 2:

A functional entity precursor carrying a hydroxy group in the position of the intended attachment to the C-F-connecting group (200 umol, 4 equiv) in a solvent such as THF, DCM, DCE, DMF, NMP or a mixture thereof (500 uL) and a base such as TEA, DIEA, pyridine (400 umol, 8 equiv), optionally in the presence of DMAP, are added to the resin bound carrier isolated in step 1 and allowed to react at temperatures between 0 °C and 100 °C, preferably between 25 °C and 80 °C, for 2-48 h, preferably.4-16 h. The resin is washed with the solvent composition used during the reaction (5x1 mL).

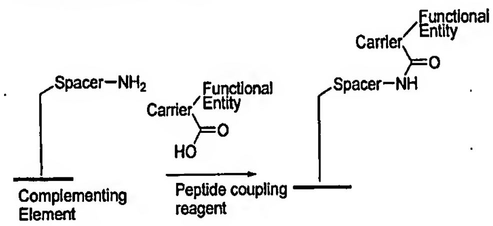
Step 3:

The desired Carrier-Functional entity reagent is cleaved from the resin obtained in step 2 by treatment with an acid like TFA, HF or HCl in a solvent such as THF, DCM, DCE or a mixture thereof (1 mL) at temperatures between -20 °C and 60 °C, preferably between 0 °C and 25 °C, for 1-4 h, preferably 1-2 h. Upon filtration, the resin is washed with the solvent composition used during cleavage (2x1 mL) and the combined filtrates are evaporated *in vacuo*. The isolated product may be purified by chromatography.

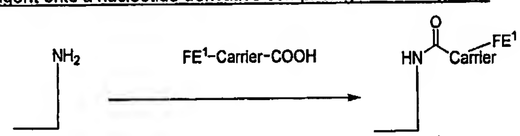
Assembly of building blocks

The Carrier-Functional entity reagent may be bound to the Spacer by several different reactions as illustrated below.

Formation of an amide bond between a carboxylic acid of the Carrier and an amine group of a Spacer

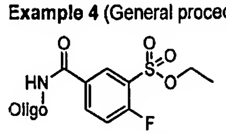


General Procedure 3: Preparation of building blocks by loading a Carrier-Functional entity reagent onto a nucleotide derivative comprising an amino group:



15 µL of a 150 mM building block solution of FE^1-Carrier-COOH is mixed with 15 µL of a 150 mM solution of EDC and 15 µL of a 150 mM solution of N-hydroxy-succinimide (NHS) using solvents like DMF, DMSO, water, acetonitril, THF, DCM, methanol, ethanol or a mixture thereof. The mixture is left for 15 min at 25°C. 45 µL of an aminooligo (10 nmol) in 100 mM buffer at a pH between 5 and 10, preferably 6.0-7.5 is added and the reaction mixture is left for 2 hours at 25°C. Excess building block and organic by-products were removed by extraction with EtOAc (400 µL). Remaining EtOAc is evaporated *in vacuo* using a speedvac. The building block is purified following elution through a BioRad micro-spin chromatography column, and analyzed by electron spray mass spectrometry (ES-MS).

Example 4 (General procedure ())



Where Oligo is 5' XCG ATG GAT GCT CCA GGT CGC 3', X = 5' amino C6 (Glen catalogue# 10-1906-90), Expected molecular weight: 6313.22

MS (calc.) = 6543,43; MS (found) = 6513,68*

* Observed molecular weight of the cleaved sulfonic ester: 6513.68 Expected molecular weight of the cleaved ester: 6514.37 The quantitative loss of the ethyl group is probably due to the presence of piperidine during the recording of the LC-MS data.

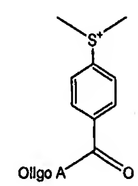
General Procedure 4: Loading of a carrier coupled functional entity onto an amino oligo:

25 µl 100 mM carrier coupled functional entity dissolved in DMF (dimethyl formamide) was mixed with 25 µl 100 mM EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) in DMF for 30 minutes at 25° C. The mixture was added to 50 µl amino oligo in H_2O with 100 mM HEPES (2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethanesulfonic acid) pH 7.5 and the reaction was allowed to proceed for 20 minutes at 25° C. Unreacted carrier coupled functional entity was removed by extraction with 500 µl EtOAc (ethyl acetate), and the oligo was purified by gel filtration through a microspin column equilibrated with 100 mM MES (2-(N-morpholino) ethanesulfonic acid) pH 6.0.

Oligonucleotide used:
Oligo A: 5'-YACGATGGATGCTCCAGGTCGC
Y = Amino modifier C6 (Glen# 10-1906)

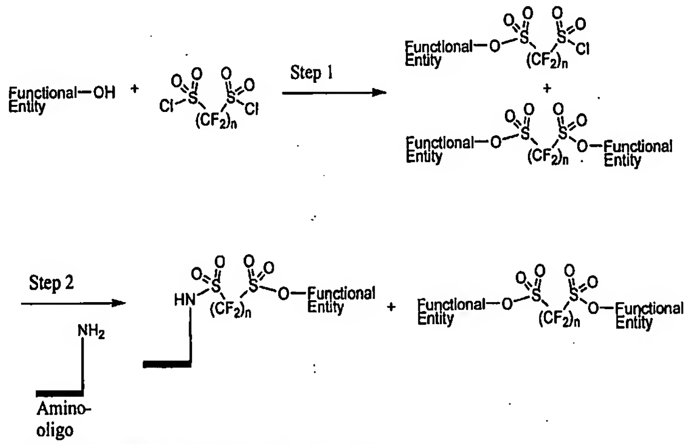
Example 5 (General procedure 4)

Carrier - Functional Entity: (4-Carboxy-phenyl)-dimethyl-sulfonium



Mass: 6789.21 (observed using ES-MS), 6790.65 (calculated)

General Procedure 5: Preparation of arylation building blocks:



Funtional Entity-OH is a phenol, n is an integer between 3 and 6.

Step 1

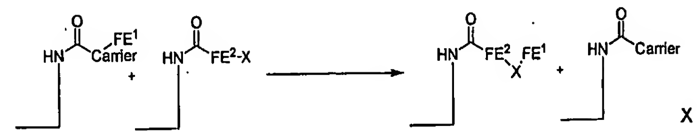
To a solution of the bis-sulfonylchloride (Ward,R.B.; J.Org.Chem.; 30; 1965; 3009-3011; Qiu, Weiming; Burton, Donald J.; J.Fluorine Chem.; 60; 1; 1993; 93-100) (3 umol) in DMF, DMSO, acetonitril, THF or a mixture thereof (150 uL) is a phenolic functional entity in excess (1.05-1.8 mmol) in DMF, DMSO, acetonitril, THF or a mixture thereof (150 uL) added slowly at temperatures between -20 °C and 100 °C preferably at 0-50 °C in the presence of a base such as TEA, DIEA, pyridine, $NaHCO_3$ or K_2CO_3.

Step2

The reaction mixture from step 1 is added to a solution of an aminooligo (10 nmol) in 100 mM buffer at a pH between 5 and 10, preferably 6.0-7.5 optionally in the presence of NHS. The reaction mixture is left for 2 hours at 25°C. Excess building block and organic by-products were removed by extraction with EtOAc (400 µL). Remaining EtOAc is evaporated *in vacuo* using a speedvac. The building aminooligo is purified following elution through a BioRad micro-spin chromatography column, and analyzed by electron spray mass spectrometry (ES-MS).

Use of building blocks

General Procedure 6: Alkylation of oligonucleotide derivatives containing a nucleophilic recipient group using a building block of the invention:



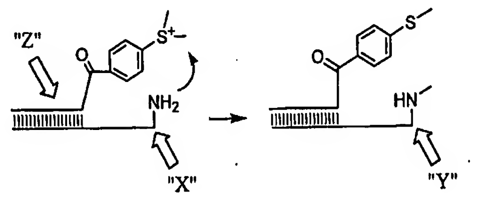
=recipient reactive group

An oligonucleotide building block carrying functional entity FE^1 is combined at 2 µM final concentration with one equivalent of a complementary building block displaying a nucleophilic recipient group. Reaction proceeds at temperatures between 0 °C and 100 °C preferably between 15 °C-50 °C for 1-48 hours, preferably 10-20 hours in DMF, DMSO, water, acetonitril, THF, DCM, methanol, ethanol or a mixture thereof, pH buffered to 4-10, preferably 6-8. Organic by-products are removed by extraction with EtOAc, followed by evaporation of residual organic solvent for 10 min *in vacuo*. Pd catalyst is removed and oligonucleotides are isolated by eluting sample through a BioRad micro-spin chromatography column. Coupling efficiency is quantified by ES-MS analysis.

General procedure 7: Transfer of functional entity from a carrier oligo to recipient reactive group.

A carrier coupled functional entity oligo (Example 1) (250 pmol) was added to a scaffold oligo B (200 pmol) in 50 µl 100 mM MES, pH 6. The mixture was incubated overnight at 25 °C. Subsequently, the mixture was purified by gel filtration using a microspin column equilibrated with H_2O and transfer of the functional entity was verified by electron spray mass spectrometry (ES-MS). Transfer efficiency is expressed in percent and were calculated by dividing the abundance of scaffold oligo carrying transferred functional entities to total abundance of scaffold oligos (with and without transferred functional entities).

Example 6 (General procedure 7)



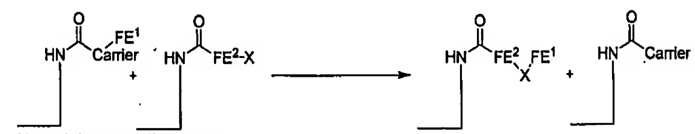
Mass ("X"): 6583.97 (observed), 6583.31 (calculated). Abundance: 65.79 (arbitrary units)

Mass ("Y"): 6599.73 (observed), 6597.34 (calculated). Abundance: 29.23 (arbitrary units)

Mass ("Z"): 6789.36 (observed), 6790.65 (calculated)

Transfer efficiency calculated as: 29.23 / (29.23 + 65.79) = 0.3076 ~ 31 %

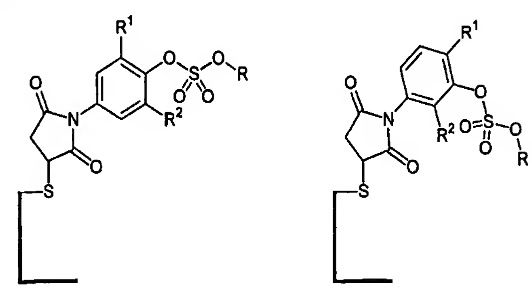
General Procedure 8: Arylation of oligonucleotide derivatives containing a nucleophilic recipient group using a building block of the invention:



X=recipient reactive group

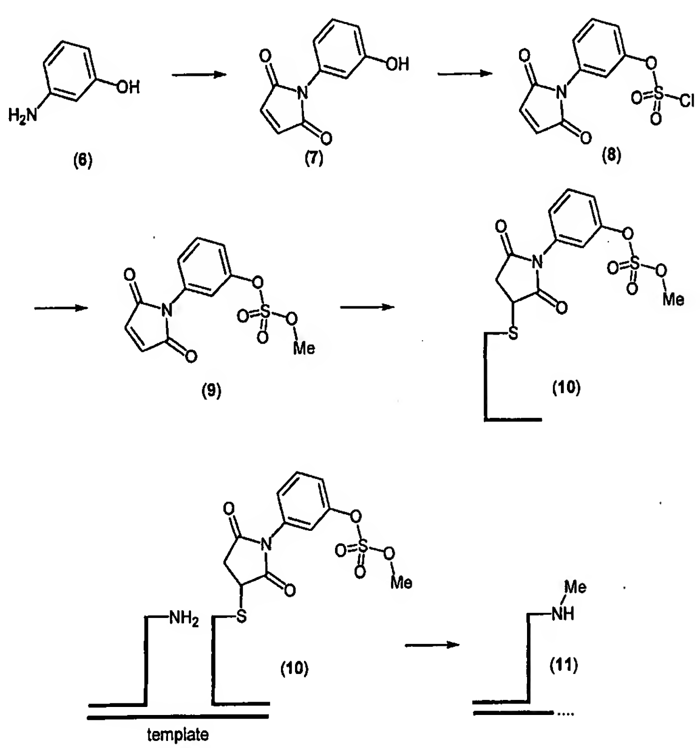
An oligonucleotide building block carrying functional entity FE^1 is combined at 2 μM final concentration with one equivalent of a complementary building block displaying a nucleophilic recipient group. In the presence of a Pd catalyst, the reaction proceeds at temperatures between 0 °C and 100 °C preferably between 15 °C-50 °C for 1-48 hours, preferably 10-20 hours in DMF, DMSO, water, acetonitrile, THF, DCM, methanol, ethanol or a mixture thereof, pH buffered to 4-10, preferably 6-8. Organic by-products are removed by extraction with EtOAc, followed by evaporation of residual organic solvent for 10 min *in vacuo*. Pd catalyst is removed and oligonucleotides are isolated by eluting sample through a BioRad micro-spin chromatography column. Coupling efficiency is quantified by ES-MS analysis.

General Procedure 9: General route to the formation of alkylating/vinylating monomer building blocks with a thio-succinimid S-C-connecting group and use of these:



R^1 = H, Me, Et, iPr, Cl, NO_2
R^2 = H, Me, Et, iPr, Cl, NO_2

R^1 and R^2 may be used to tune the reactivity of the sulphate to allow appropriate reactivity. Chloro and nitro substitution will increase reactivity. Alkyl groups will decrease reactivity. Ortho substituents to the sulphate will due to steric reasons direct incoming nucleophiles to attack the R-group selectively and avoid attack on sulphur. E.g.



3-Aminophenol (**6**) is treated with maleic anhydride, followed by treatment with an acid e.g. H_2SO_4 or P_2O_5 and heat to yield the maleimide (**7**). The ring closure to the maleimide may also be achieved when an acid stable *O*-protection group is used by treatment with or Ac_2O with or without heating, followed by *O*-deprotection. Alternatively reflux in Ac_2O, followed by *O*-deacetylation in hot water/dioxane to yield (**7**).

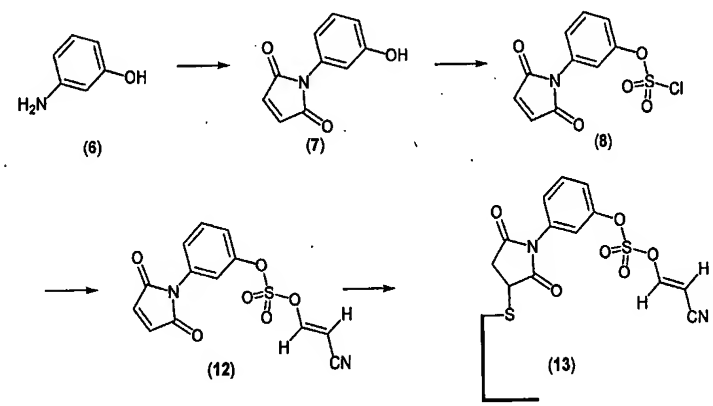
Further treatment of (**7**) with SO_2Cl_2 with or without triethylamine or potassium carbonate in dichloromethane or a higher boiling solvent will yield the intermediate (**8**), which may be isolated or directly further transformed into the aryl alkyl sulphate by the quench with the appropriate alcohol, in this case MeOH, whereby (**9**) will be formed. The organic building block (**9**) may be connected to an oligo nucleotide, as follows.

A thiol carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic building block (**9**) in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C. To give the alkylating in this case methylating monomer building block (**10**).

The reaction of the alkylating monomer building block (**10**) with an amine carrying monomer building block may be conducted as follows:

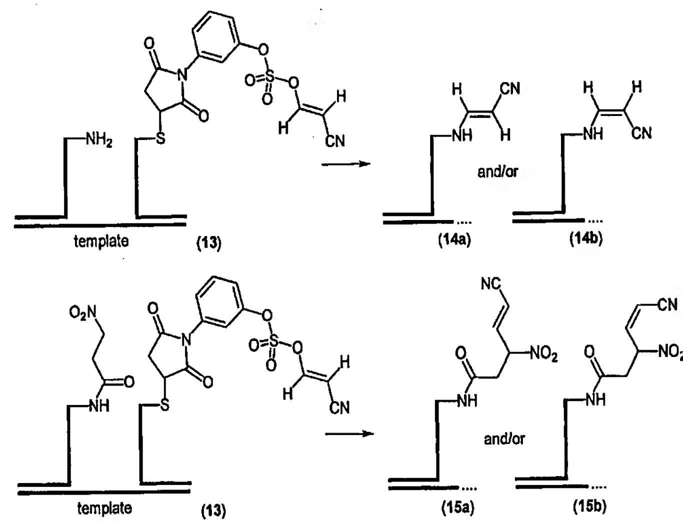
The coding oligonucleotide (1 nmol) is mixed with a thio oligonucleotide loaded with a building block (1 nmol) (**10**) and an amino-oligonucleotide (1 nmol) in hepes-buffer (20 µL of a 100 mM hepes and 1 M NaCl solution, pH=7.5) and water (39 uL). The oligonucleotides are annealed to the template by heating to 50 °C and cooled (2 °C/second) to 30 °C. The mixture is then left o/n at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second), to yield the template bound methylamine (**11**).

A vinylating monomer building block may be prepared and used similarily as described above for an alkylating monomer building block. Although instead of reacting the chlorosulphonate (**8** above) with an alcohol, the intermediate chlorosulphate is isolated and treated with an enolate or *O*-trialkylsilylenolate with or without the presence of fluoride. E.g.


(6) (7) (8) (12) (13)

Formation of the vinylating monomer building block (**13**):
The thiol carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic building block (**12**) in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C. To give the vinylating monomer building block (**13**).

The sulfonylenolate (**13**) may be used to react with amine carrying monomer building block to give an enamine (**14a** and/or **14b**) or e.g. react with an carbanion to yield (**15a** and/or **15b**). E.g.



(13) (14a) (14b) (13) (15a) (15b)

The reaction of the vinylating monomer building block (**13**) and an amine or nitroalkyl carrying monomer building block may be conducted as follows:
The coding oligonucleotide (1 nmol) is mixed with a oligonucleotide building block (1 nmol) (**13**) and an amino-oligonucleotide (1 nmol) or nitroalkyl-oligonucleotide (1 nmol) in 0.1 M TAPS, phosphate or hepes-buffer and 300 mM NaCl solution, pH=7.5-8.5 and preferably pH=8.5. The oligonucleotides are annealed to the template by heating to 50 °C and cooled (2 °C/ second) to 30 °C. The mixture is then left o/n at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second), to yield template bound (**14a/b** or **15a/b**).

Abbreviations

DCC	N,N'-Dicyclohexylcarbodiimide
DhbtOH	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
DIC	Diisopropylcarbodiimide
DIEA	Diethylisopropylamin
DMAP	4-Dimethylaminopyridine

DNA	Deoxyribosenucleic Acid
EDC	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide·HCl
HATU	2-(1*H*-7-Azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt	N-Hydroxy-7-azabenzotriazole
HOBt	N-Hydroxybenzotriazole
LNA	Locked Nucleic Acid
NHS	N-hydroxysuccinimid
OTf	Trifluoromethylsulfonate
OTs	Toluenesulfonate
PNA	Peptide Nucleic Acid
PyBoP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
RNA	Ribonucleic acid
TBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
TBDMS-Cl	*Tert*-Butyldimethylsilylchloride
5-Iodo-dU	5-iodo-deoxyriboseuracil
TLC	Thin layer chromatography
$(Boc)_2O$	Boc anhydride, di-*tert*-butyl dicarbonate
TBAF	Tetrabutylammonium fluoride
SPDP	Succinimidyl-propyl-2-dithiopyridyl

Claims

1. A building block of the general formula

Complementing Element – Linker – Carrier – C-F-connecting group - Functional entity precursor

capable of transferring a Functional entity precursor to a recipient reactive group, wherein

Complementing Element is a group identifying the Functional entity precursor,

Linker is a chemical moiety comprising a **spacer** and a **S-C-connecting group**, wherein the spacer is a valence bond or a group distancing the Functional entity precursor to be transferred from the complementing element and the S-C-connecting group connects the spacer with the Carrier

Carrier is arylene, heteroarylene, C_1-C_6 alkylene, C_1-C_6 alkenylene, C_1-C_6 alkynylene, or -$(CF_2)_m$- substituted with 0-3 R^1 wherein m is an integer between 1 and 10;

R^1 are independently selected from -H, -OR^2, -NR^2_2, -Halogen, -NO_2, -CN, -C(Halogen)$_3$, -C(O)R^2, -C(O)NHR^2, C(O)NR^2_2, -NC(O)R^2, -S(O)$_2NHR^2$, -S(O)$_2NR^2_2$, -S(O)$_2R^2$, –P(O)$_2$-R^2, –P(O)- R^2, –S(O)- R^2, P(O)-OR^2, –S(O)-OR^2, -$N^+R^2_3$, wherein

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl,

C-F-connecting group is chosen from the group consisting of –SO_2-O-, -O-SO_2-O-, -C(O)-O-, -$S^+(R^3)$-, -C-U-C(V)-O-, -$P^+(W)_2$-O-, -P(W)-O- where U is -$C(R^2)_2$-, -NR^2- or –O-; V is =O or =NR^2 and W is -OR^2 or –$N(R^2)_2$

Functional entity precursor is -C(H)(R^3)-R^4 or functional entity precursor is heteroaryl or aryl optionally substituted with one or more substituents belonging to the group comprising R^3 and R^4.

Wherein R^3 and R^4 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $SnR^5R^6R^7$, $Sn(OR^5)R^6R^7$, $Sn(OR^5)(OR^6)R^7$, BR^5R^6, $B(OR^5)R^6$, $B(OR^5)(OR^6)$, halogen, CN, CNO, C(halogen)$_3$, OR^5, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, SR^5, $S(=O)R^5$, $S(=O)_2R^5$, $S(=O)_2NR^5R^6$, NO_2, N_3, NR^5R^6, $N^+R^5R^6R^7$, NR^5OR^6, $NR^5NR^6R^7$, $NR^5C(=O)R^6$, $NR^5C(=O)OR^6$, $NR^5C(=O)NR^6R^7$, NC, $P(=O)(OR^5)OR^6$, $P^+R^5R^6R^7$, $C(=O)R^5$,

C(=NR^5)R^6, C(=NOR^5)R^6, C(=NNR^{5}R^6), C(=O)OR^5, C(=O)NR^{5}R^6, C(=O)NR^{5}OR^6, C(=O)NR^{5}NR^{6}R^7, C(=NR^5)NR^{6}R^7, C(=NOR^5)NR^{6}R^7 or R^8,

wherein,

R^5, R^6, and R^7 independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CNO, C(halogen)$_3$, =O, OR^8, OC(=O)R^8, OC(=O)OR^8, OC(=O)NR^{8}R^9, SR^8, S(=O)R^8, S(=O)$_2$R^8, S(=O)$_2$NR^{8}R^9, NO$_2$, N$_3$, NR^{8}R^9, N$^+$R^{8}R^{9}R^{10}, NR^{5}OR^6, NR^{5}NR^{6}R^7, NR^{8}C(=O)R^9, NR^{8}C(=O)OR^9, NR^{8}C(=O)NR^{9}R^{10}, NC, P(=O)(OR^8)OR^9, P$^+$R^{5}R^{6}R^7, C(=O)R^8, C(=NR^8)R^9, C(=NOR^8)R^9, C(=NNR^{8}R^9), C(=O)OR^8, C(=O)NR^{8}R^9, C(=O)NR^{8}OR^9 C(=NR^5)NR^{6}R^7, C(=NOR^5)NR^{6}R^{7}or C(=O)NR^{8}NR^{9}R^{10}, wherein R^5 and R^6 may together form a 3-8 membered heterocyclic ring or R^5 and R^7 may together form a 3-8 membered heterocyclic ring or R^6 and R^7 may together form a 3-8 membered heterocyclic ring,

wherein,

R^8, R^9, and R^{10} independently is H, alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloheteroalkyl, aryl or heteroaryl and wherein R^8 and R^9 may together form a 3-8 membered heterocyclic ring or R^8 and R^{10} may together form a 3-8 membered heterocyclic ring or R^9 and R^{10} may together form a 3-8 membered heterocyclic ring.

2. A compound according to claim 1 wherein, **Functional entity precursor** is -C(H)(R^{11})-R$^{11'}$ or functional entity precursor is heteroaryl or aryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3 R^{15}, wherein

R^{11} and R$^{11'}$ are independently H, or selected among the group consisting of a C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_4$-C$_8$ alkadienyl, C$_3$-C$_7$ cycloalkyl, C$_3$-C$_7$ cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^{12}, 0-3 R^{13} and 0-3 R^{15},

or R^{11} and R$^{11'}$ are C$_1$-C$_3$ alkylene-NR$^{12}{}_2$, C$_1$-C$_3$ alkylene-NR^{12}C(O)R^{16}, C$_1$-C$_3$ alkylene-NR^{12}C(O)OR^{16}, C$_1$-C$_2$ alkylene-O-NR$^{12}{}_2$, C$_1$-C$_2$ alkylene-O-NR^{12}C(O)R^{16}, C$_1$-C$_2$ alkylene-O-NR^{12}C(O)OR^{16} substituted with 0-3 R^{15},

where R^{12} is H or selected independently among the group consisting of C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_7$ cycloalkyl, C$_3$-C$_7$ cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{13} and 0-3 R^{15},

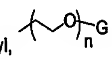
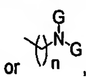
R^{13} is selected independently from -N$_3$, -CNO, -C(NOH)NH$_2$, -NHOH, -NHNHR^{17}, -C(O)R^{17}, -SnR$^{17}{}_3$, -B(OR^{17})$_2$, -P(O)(OR^{17})$_2$ or the group consisting of

C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_4$-C$_8$ alkadienyl said group being substituted with 0-2 R^{14},

where R^{14} is independently selected from –NO$_2$, -C(O)OR^{17}, -COR^{17}, -CN, -OSiR$^{17}{}_3$, -OR^{17} and -NR$^{17}{}_2$;

R^{15} is =O, -F, -Cl, -Br, -I, -CN, -NO$_2$, -OR^{17}, -NR$^{17}{}_2$, -NR^{17}-C(O)R^{16}, -NR^{17}-C(O)OR^{16}, -SR^{17}, -S(O)R^{17}, -S(O)$_2$R^{17}, -COOR^{17}, -C(O)NR$^{17}{}_2$ and -S(O)$_2$NR$^{17}{}_2$,

R^{16} is H, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_7$ cycloalkyl, aryl or C$_1$-C$_6$ alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, –NO$_2$, -R^2, -OR^2, -SiR$^2{}_3$;

R^{17} is selected independently from H, C$_1$-C$_6$ alkyl, C$_3$-C$_7$ cycloalkyl, aryl, C$_1$-C$_6$ alkylene-aryl,  or , G is H or C$_1$-C$_6$ alkyl and n is 1,2,3 or 4.

3. A compound according to claim 2 wherein, **Functional entity precursor** is -C(H)(R^{11})-R$^{11'}$ or functional entity precursor is heteroaryl or aryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3 R^{15}, wherein

R^{11} and R$^{11'}$ are independently H, or selected among the group consisting of a C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_4$-C$_8$ alkadienyl, C$_3$-C$_7$ cycloalkyl, C$_3$-C$_7$ cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^{12}, 0-3 R^{13} and 0-3 R^{15},

or R^{11} and R$^{11'}$ are C$_1$-C$_3$ alkylene-NR$^{12}{}_2$, C$_1$-C$_3$ alkylene-NR^{12}C(O)R^{16}, C$_1$-C$_3$ alkylene-NR^{12}C(O)OR^{16}, C$_1$-C$_2$ alkylene-O-NR$^{12}{}_2$, C$_1$-C$_2$ alkylene-O-NR^{12}C(O)R^{16}, C$_1$-C$_2$ alkylene-O-NR^{12}C(O)OR^{16} substituted with 0-3 R^{15},

where R^{12} is H or selected independently among the group consisting of C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_7$ cycloalkyl, C$_3$-C$_7$ cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^{13} and 0-3 R^{15},

R^{13} is selected independently from -N$_3$, -CNO, -C(NOH)NH$_2$, -NHOH, -NHNHR^{17}, -C(O)R^{17}, -SnR$^{17}{}_3$, -B(OR^{17})$_2$, -P(O)(OR^{17})$_2$ or the group consisting of C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_4$-C$_8$ alkadienyl said group being substituted with 0-2 R^{14},

where R^{14} is independently selected from –NO$_2$, -C(O)OR^{17}, -COR^{17}, -CN, -OSiR$^{17}{}_3$, -OR^{17} and -NR$^{17}{}_2$;

R^{15} is =O, -F, -Cl, -Br, -I, -CN, -NO$_2$, -OR^{17}, -NR$^{17}{}_2$, -NR^{17}-C(O)R^{16}, -NR^{17}-C(O)OR^{16}, -SR^{17}, -S(O)R^{17}, -S(O)$_2$R^{17}, -COOR^{17}, -C(O)NR$^{17}{}_2$ and -S(O)$_2$NR$^{17}{}_2$,

R^{16} is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, –NO_2, -R^2, -OR^2, -SiR^2_3;
wherein R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl.

4. A compound according to claim 1 wherein, **Functional entity precursor** is -C(H)(R^{11})-$R^{11'}$ wherein
R^{11} and $R^{11'}$ are or C_1-C_3 alkylene-NR^{12}_2, C_1-C_3 alkylene-$NR^{12}C(O)R^{16}$, C_1-C_3 alkylene-$NR^{12}C(O)OR^{16}$, C_1-C_2 alkylene-O-NR^{12}_2, C_1-C_2 alkylene-O-$NR^{12}C(O)R^{16}$, C_1-C_2 alkylene-O-$NR^{12}C(O)OR^{16}$ substituted with 0-3 R^{15}

5. A compound according to claim 1 wherein, **Functional entity precursor** is -C(H)(R^{11})-$R^{11'}$ wherein
R^{11} and $R^{11'}$ are independently H, or selected among the group consisting of a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^{12}, 0-3 R^{13} and 0-3 R^{15},

6. A compound according to claim 2 wherein, **Functional entity precursor** is -C(H)(R^{11})-$R^{11'}$ wherein
R^{11} and $R^{11'}$ are independently H, or selected among the group consisting of a C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^{12} and 0-3 R^{15},
where R^{12} is H or selected independently among the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl.
R^{15} is =O, -F, -Cl, -Br, -I, -CN, -NO_2, -OR^{17}, -NR^{17}_2, -NR^{17}-C(O)R^{16}, -NR^{17}-C(O)OR^{16}, -SR^{17}, -S(O)R^{17}, -S(O)$_2R^{17}$, -COOR^{17}, -C(O)NR^{17}_2 and -S(O)$_2NR^{17}_2$, R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 alkylene-aryl,

7. A compound according to claim 1 wherein, **Functional entity precursor** is heteroaryl or aryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3

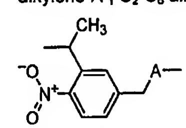
8. A compound according to claim 2 wherein **C-F-connecting group** is chosen from the group consisting of –SO_2-O-, -O-SO_2-O-, -C(O)-O-, -S^+(R^{11})-, -C-U-C(V)-O-, -P^+(W)$_2$-O-, and -P(W)-O- where U is -C(R^2)$_2$-, -NR^2- or –O-; V is =O or =NR^2 and W is -OR^2 or –N(R^2)$_2$

9. A compound according to claim 2 wherein **C-F-connecting group** is -S^+(R^{11})-,

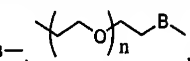
10. A compound according to claims 1 - 2 wherein **C-F-connecting group** is chosen from the group consisting of –SO_2-O-, -O-SO_2-O-, -C(O)-O-, -S^+(R^{17})-, -C-U-C(V)-O-, -P^+(W)$_2$-O-, and -P(W)-O- where U is -C(R^2)$_2$-, -NR^2- or –O-; V is =O or =NR^2 and W is -OR^2 or –N(R^2)$_2$, wherein R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl.

11. A compound according to claims 1 - 2 wherein **C-F-connecting group** is chosen from the group consisting of –SO_2-O-, and -S^+(R^{17})-; wherein R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 alkylene-aryl.

12. A compound according to claim 1 wherein, **Spacer** is a valence bond, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, C_2-C_6 alkynylene-A-, or



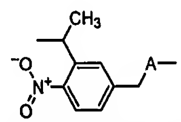
said spacer optionally being connected through A to a linker selected from

—$(CH_2)_n$–B—,  , and

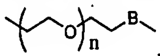
—$(CH_2)_n$–S–S–$(CH_2)_m$–B—

where A is a valence bond, –C(O)NR^{17}-, -NR^{17}-, -O-, -S-, or -C(O)-O-; B is a valence bond, -O-, -S-, –NR^{17}- or –C(O)NR^{17}- and connects to S-C-connecting group; and n and m independently are integers ranging from 1 to 10; and R^{17} is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl, or C_1-C_6 alkylene-aryl

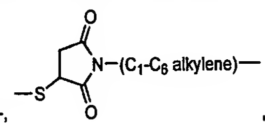
13. A compound according to claim 1 wherein, **Spacer** is a valence bond, C_1-C_6 alkylene-A-, C_2-C_6 alkenylene-A-, C_2-C_6 alkynylene-A-, or

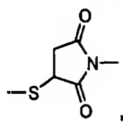


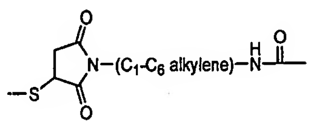
said spacer optionally being connected through A to a linker selected from

—$(CH_2)_n$–B—,  , and

where A is a valence bond, –C(O)NR^{17}-, -NR^{17}-, -S-, or -C(O)-O-; B is -O-, -S-, -NR^{17}-, or –C(O)NR^{17}- and connects to S-C-connecting group; and n and m independently are integers ranging from 1 to 6; and R^{17} is selected independently from H, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, aryl, or C_1-C_6 alkylene-aryl

14. A compound according to claim 1-2 wherein, **S-C-connecting group** is a valence bond, –NH-C(=O)-, –NH-SO_2-, -S-S-,  ,

 , -C(=O)-NH-, or



15. A compound according to claim 2 wherein, the carrier is selected from the group consisting of arylene, heteroarylene or -$(CF_2)_m$- substituted with 0-3 R^1 wherein m is an integer between 1 and 10, and C-F-connecting group is –SO_2-O-, and the functional entity precursor is -C(H)(R^{11})-R$^{11'}$.

16. A compound according to claim 2 wherein, the carrier is -$(CF_2)_m$- wherein m is an integer between 1 and 10, the C-F-connecting group is –SO_2-O-; and the functional entity precursor is aryl or heteroaryl substituted with 0-3 R^{11}, 0-3 R^{13} and 0-3 R^{15}.

17. A compound according to claims 1-16 wherein Complementing element is a nucleic acid.

18. A compound according to claims 1-16 where Complementing element is a sequence of nucleotides selected from the group of DNA, RNA, LNA PNA, or morpholino derivatives.

19. A library of compounds according to claim 1, wherein each different member of the library comprises a complementing element having a unique sequence of nucleotides, which identifies the functional entity.

20. A method for transferring a functional entity precursor to a recipient reactive group, comprising the steps of

providing one or more building blocks according to claims 1 to 18,

contacting the one or more building blocks with a corresponding encoding element associated with a recipient reactive group under conditions which allow for a recognition between the one or more complementing elements and the encoding elements, said contacting being performed prior to, simultaneously with, or subsequent to a transfer of the functional entity precursor to the recipient reactive group.

21. The method according to claim 20, wherein the encoding element comprises one or more encoding sequences comprised of 1 to 50 nucleotides and the one or more complementing elements comprises a sequence of nucleotides complementary to one or more of the encoding sequences.

22. The method of claims 20 or 21, wherein the recipient reactive group is a nucleophilic S- or N- atom, which may be part of a chemical scaffold, and the activating catalyst is contains palladium.

Figure 1. Two setups for Functional Entity Transfer

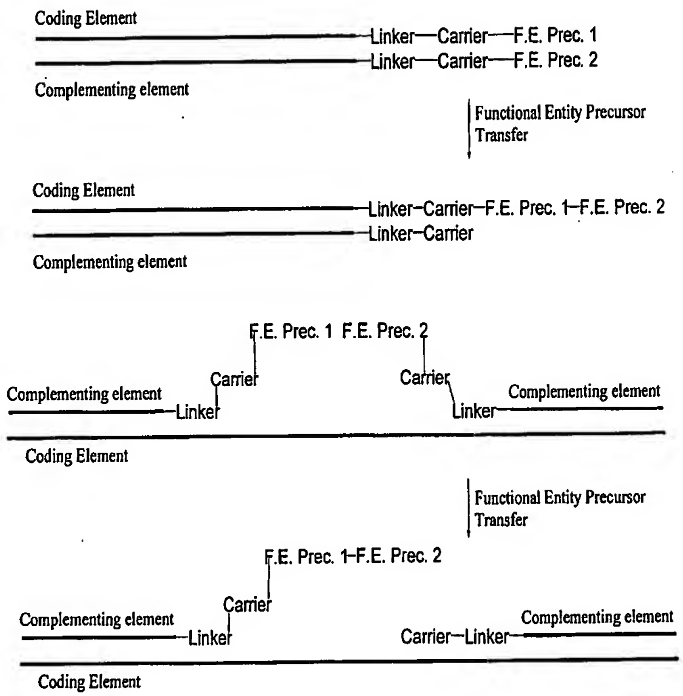
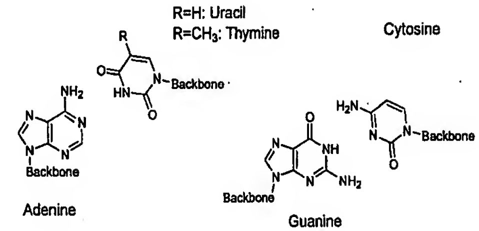
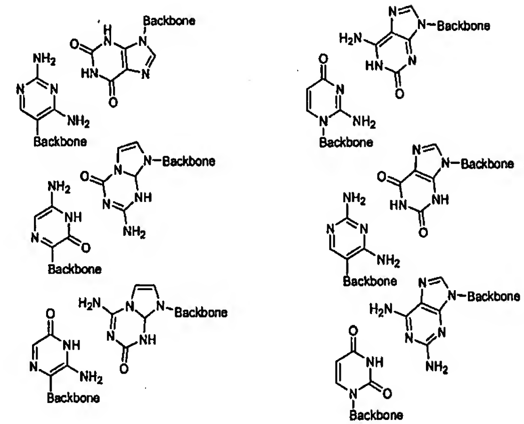


Figure 2. Examples of specific base pairing

Natural Base Pairs



Synthetic Base Pairs



Synthetic purine's base pairing with U/T or C

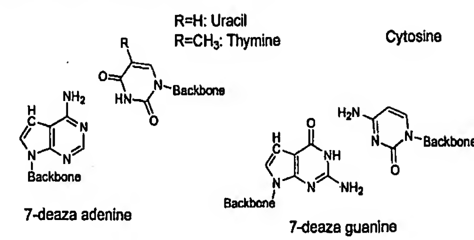


Figure 3. Example of non-specific base-pairing

I = Inosine

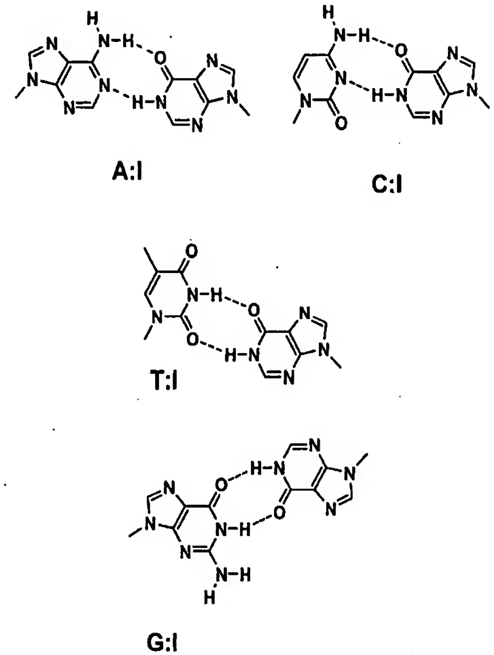


Figure 4. Backbone examples

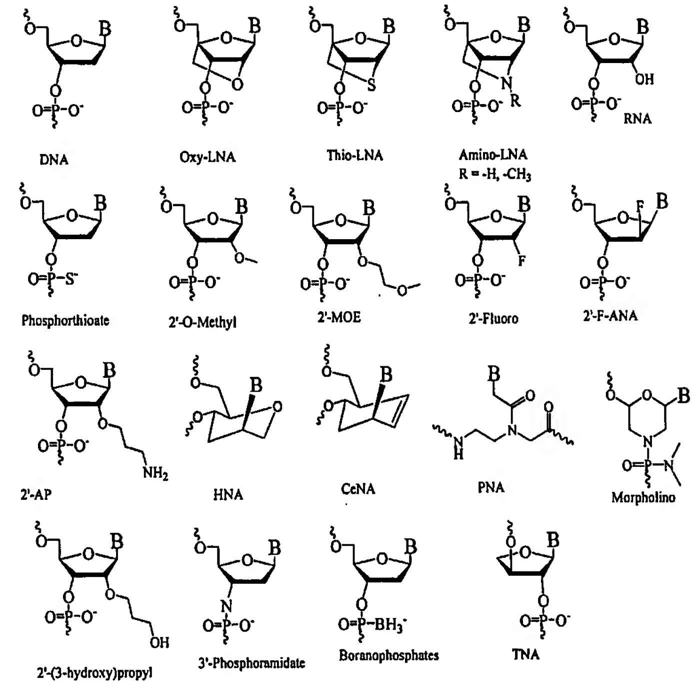
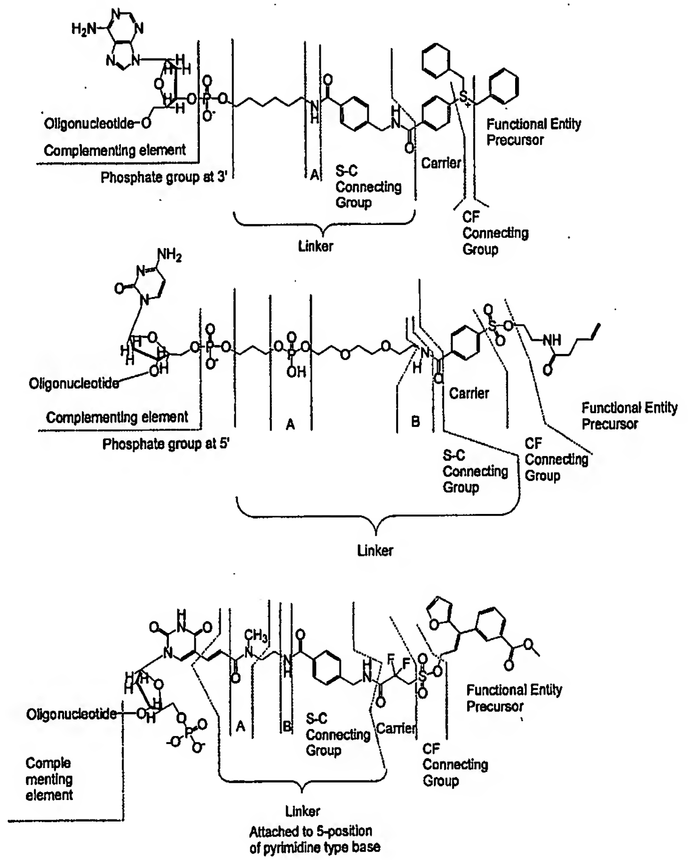


Figure 5.



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60/434,423	19 December 2002 (19.12.2002)	US

(71) Applicant *(for all designated States except US)*: NUEVOLUTION A/S [DK/DK]; Rønnegade 8, 5th floor, DK-2100 Copenhagen Ø (DK).

(72) Inventors; and
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/078446 A3

(54) Title: A BUILDING BLOCK FORMING A C-C OR A C-HETERO ATOM BOND UPONREACTION

(57) Abstract: A building block having the dual capabilities of transferring genetic information and functional entity precursor to a recipient reactive group is disclosed. The building block may be used in the generation of a single complex or libraries of different complexes, wherein the complex comprises an encoded molecule linked to an encoding element. Libraries of complexes are useful in the quest for pharmaceutically active compounds.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 02895 A (THOMPSON ANDREW HUGIN ;BRAX GROUP LTD (GB); SCHMIDT GUENTER (GB);) 20 January 2000 (2000-01-20) the whole document ---	1
A	WALDER J A ET AL: "COMPLEMENTARY CARRIER PEPTIDE SYNTHESIS: GENERAL STRATEGY AND IMPLICATIONS FOR PREBIOTIC ORIGIN OF PEPTIDE SYNTHESIS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 76, no. 1, January 1979 (1979-01), pages 51-55, XP000857351 ISSN: 0027-8424 the whole document ---	20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2003	06/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00176

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRUICK R K ET AL: "TEMPLATE-DIRECTED LIGATION OF PEPTIDES TO OLIGONUCLEOTIDES" CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 3, no. 1, January 1996 (1996-01), pages 49-56, XP000856876 ISSN: 1074-5521 the whole document ----	20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00176

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-22 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International Application No. PCT/DK 03/00176

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-22 (in part)

Present claims 1-22 relate to an extremely large number of possible building blocks. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Furthermore, support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the building blocks claimed. Consequently, the search has been carried out for those parts of the application which do appear to be clear, supported and disclosed, namely those parts related to the building blocks of claim 1 where the complementing element is a nucleic acid or a derivative thereof as in claims 17 and 18 AND where the C-F connecting group is $-SO_2-O-$ or $-S+(R3)-$ with R3 defined in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00176

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0002895 A	20-01-2000	AT 237626 T	15-05-2003
		AT 229537 T	15-12-2002
		AU 1770499 A	12-07-1999
		AU 4921099 A	01-02-2000
		CA 2337761 A1	20-01-2000
		CA 2385987 A1	20-01-2000
		DE 69813622 D1	22-05-2003
		DE 69904478 D1	23-01-2003
		DK 1042345 T3	11-08-2003
		DK 1095053 T3	07-04-2003
		EP 1042345 A1	11-10-2000
		EP 1095053 A1	02-05-2001
		ES 2189443 T3	01-07-2003
		WO 9932501 A1	01-07-1999
		WO 0002895 A1	20-01-2000
		GB 2340602 A	23-02-2000
		JP 2002520580 T	09-07-2002
		NZ 509518 A	25-07-2003
		PT 1095053 T	30-04-2003
		US 6287780 B1	11-09-2001

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(72) Inventors; and
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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/078446 A2

(54) Title: A BUILDING BLOCK FORMING A C-C OR A C-HETERO ATOM BOND UPONREACTION

(57) Abstract: A building block having the dual capabilities of transferring genetic information and functional entity precursor to a recipient reactive group is disclosed. The building block may be used in the generation of a single complex or libraries of different complexes, wherein the complex comprises an encoded molecule linked to an encoding element. Libraries of complexes are useful in the quest for pharmaceutically active compounds.

Title

A BUILDING BLOCK FORMING A C-C OR C-HETERO ATOM BOND UPON REACTION.

Technical Field of the Invention

The present invention relates to a building block comprising a complementing element and a precursor for a functional entity. The building block is designed to transfer the functional entity precursor with an adjustable efficiency to a recipient reactive group upon recognition between the complementing element and an encoding element associated with the reactive group. The invention also relates to a method for transferring a functional entity precursor to recipient a reactive group.

Background

The transfer of a chemical entity from one mono-, di- or oligonucleotide to another has been considered in the prior art. Thus, N. M. Chung *et al.* (Biochim. Biophys. Acta,1971, 228,536-543) used a poly(U) template to catalyse the transfer of an acetyl group from 3'-O-acetyladenosine to the 5'-OH of adenosine. The reverse transfer, i.e. the transfer of the acetyl group from a 5'-O-acetyladenosine to a 3'-OH group of another adenosine, was also demonstrated.

Walder *et al.* Proc. Natl. Acad. Sci. USA, 1979, 76, 51-55 suggest a synthetic procedure for peptide synthesis. The synthesis involves the transfer of nascent immobilized polypeptide attached to an oligonucleotide strand to a precursor amino acid attached to an oligonucleotide. The transfer comprises the chemical attack of the amino group of the amino acid precursor on the substitution labile peptidyl ester, which in turn results in an acyl transfer. It is suggested to attach the amino acid precursor to the 5' end of an oligonucleotide with a thiol ester linkage.

The transfer of a peptide from one oligonucleotide to another using a template is disclosed in Bruick RK et al. Chemistry & Biology, 1996, 3:49-56. The carboxy terminal of the peptide is initially converted to a thioester group and subsequently transformed to an activated thioester upon incubation with Ellman's reagent. The activated thioester is reacted with a first oligo, which is 5'-thiol-terminated, resulting in the formation of a thio-ester linked intermediate. The first oligonucleotide and a